PERCHLORATES

Their
Properties, Manufacture and Uses

Edited by

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10. BIOLOGICAL ACTION OF PERCHLORATES

Despite long industrial experience in the manufacture of sodium, potassium and ammonium perchlorates, there does not seem to be any evidence that exposure to at least these three perchlorates involves any appreciable biological hazard. This limited conclusion, however, should not be extrapolated to a supposition that the perchlorates are biologically inert or without hazard.

Investigations of the biological action of sodium and potassium perchlorates, the salts most studied, have revealed a number of interesting effects in both plants and animals. While these two compounds would be considered to be only "slightly toxic" to animals under the classification scheme of Hodge and Sterner,[40] both perchloryl fluoride and the nitrate ester of choline perchlorate would be rated as "moderately" toxic; other perchlorates may be still more toxic. The perchlorates, therefore, cover a broad range of biological activity. Unfortunately, only a very few of the many perchlorates known have been studied, and substantial gaps remain to be filled in before the details of their mode of action can be fully elucidated.

ACTION OF PERCHLORATES IN PLANTS

In 1896, Sjollema[73] described damage to rye crops fertilized with Chile saltpeter, which had been occurring sporadically for a number of years. He attributed this effect to potassium perchlorate present as a contaminant in the saltpeter in amounts ranging from 0 to 6.79 per cent, varying even within the same lot (see Chapter 1 regarding the origin of the perchlorate). Sjollema reported that ½ or 1 per cent of either sodium or potassium perchlorate considerably delayed rye germination and produced abnormal embryos. Rye plants grown in pots containing as little as 50 mg perchlorate showed delayed growth, were stunted and bent, and had yellowed leaves. Maercker[55] noted similar effects of perchlorate-contaminated saltpeter on rye and concluded that a perchlorate content of 1.5 per cent or less could be harmful under appropriate circumstances. For example, oats were said to be damaged by 1 per cent perchlorate. Caluwe[16] also studied the toxic effects of perchlorate in field experiments with rye.

Lauffs[50] investigated the effects of perchlorate on plants in greater detail. He found that small amounts of perchlorate stimulated growth and chlorophyll formation, but that the root hairs of wheat plants grown for 8 days in weak perchlorate solutions were often deformed, branched or strongly bent and thickened at the tip. An intensive protoplasmic streaming was seen in root hairs of the aquatic plant, *Hydrocharis morsus ranae*, after

3 weeks in 0.01 per cent perchlorate solution. Stiehr,[85] however, found that exposure of young wheat and rye plants to 0.2 to 1.0 per cent potassium perchlorate solutions for only a few hours had little effect on the root hairs.

Much heat but little light was added to these findings through an interesting exchange of somewhat personalized opinions between Sjollema[74, 75] and Verweij.[90] Their discussion was principally directed to the question of whether or not perchlorate in saltpeter was actually damaging to plants in view of its low average concentration (0.2 per cent). Lauffs' comment,[50] to the effect that small amounts of perchlorate were actually beneficial although large amounts were toxic, was cited by Verweij. Sjollema[75] appears to have had the last word in this argument. He stated that: the irregularity of perchlorate content in Chile saltpeter was due to its occurrence in pockets (*Nesten*), so that some bags were toxic while others were not; plants have a variable sensitivity to perchlorate; certain suppliers had begun (in about 1892) to use an excessive recycle of the saltpeter mother liquor with a consequent increase in perchlorate content, thus accounting for the apparently sudden appearance of the damage to crops.

Vandevelde[89] also conducted some toxicological studies in which he found that the germination of the seeds of *Pisum sativum*, after soaking 24 hr in the solutions noted, was as follows: water, 98.7 per cent; 1 per cent potassium chlorate, 93.7 per cent; 1 per cent potassium perchlorate, 97.5 per cent. Potassium and sodium perchlorates both produced plasmolysis in *Allium* cells, which could be reversed by treatment with water; the cells did not appear to be harmed.

According to Alvisi and Orabona,[2] no chloride ion could be found in mixtures of pepsin, papain or diastase with 0.2 per cent potassium perchlorate after 1 to 6 days at room temperature. *Penicillium glaucum* reduced ammonium perchlorate but not potassium perchlorate. Experiments with beans (either the whole plant or root plus stalk) indicated that, initially, solutions of potassium perchlorate were harmful, but that eventually there was a beneficial effect attributed to the disinfecting properties of the salt. With ammonium perchlorate, the anion appeared to be decomposed through an internal reaction. The perchlorate ion was thus less stable when combined with NH_4^+ than with K^+.

Maschhaupt,[58] returning to the problem of Chile saltpeter, found a maximum perchlorate content of 1.5 per cent, and about 1 per cent in refined saltpeter. He reported that, while the perchlorate disease of grains (*Getreide*) was due to an abnormally high content of perchlorate in saltpeter, the observed variability in the amount of damage was due to both the type of grain and the amount of perchlorate. Nevertheless, the growth-inhibiting action of perchlorate was always evident in his fertilization experiments, the plants also being more darkly colored than untreated ones. He thus substantiated the original findings of Sjollema.

Weiske[92] also noted similar effects on the growth and germination of grains and vegetables. He found, however, that there were only slight differences when the plants were treated with the amount of potassium perchlorate, potassium chlorate, sodium iodate or sodium periodate present in the quantity of saltpeter normally used for fertilization; the difference became appreciable when 5 to 10 times this amount was used.

Since one of the effects of perchlorate on plants is a strong bending of the shoots, probably little reliance can be placed on the measurements of plant height cited by Yamasaki[96] as evidence that 0.5 per cent perchlorate solution was more toxic than 1 per cent chlorate. Cook reported that, when sprayed on plants grown in soil, perchlorate was less toxic than chlorate,[21] although in solution culture the lethal dose was about the same (0.25 per cent) for both chlorate and perchlorate.[22] Owen[68] described a mottling of the foliage of young tomato plants as a result of either perchlorate or chlorate poisoning, but the symptoms were not the same in both cases.

Weaver[91] found that chlorate was less toxic to Biloxi soybeans than was perchlorate. Also, while chlorate was less toxic to the plants grown in water culture than to those grown in sand, the opposite was true for perchlorate. A significant difference in the effects of these two anions, noted by Weaver, was that chlorate injury began with the older leaves of the plant, while perchlorate first affected the apical meristem and younger leaves. In general, perchlorate often killed the tips of the leaflets, and the trifoliate leaves were charactertistically crumpled. At 30 ppm perchlorate (the highest concentration used), the leaves failed to expand at all; at 2.5 ppm, the first trifoliate leaves had expanded normally, the second and third sets were crumpled, and the fourth failed to expand. Terminal growth was retarded and shoots arose from the axils of the cotyledons and leaves.

In a detailed study of the effects of a number of salts on young wheat plants (*Triticum vulgare* Vill.) grown in nutrient solution, Åberg[1] observed that the toxicity of perchlorate was less than that of chlorate, and that the symptoms of poisoning by these two substances were widely different. Seedlings, grown both in the light and in darkness, exhibited a marked growth depression even at a concentration of 0.1 m*M* perchlorate, but shoot injuries appeared only above 0.5 m*M* and then only in the light-grown plants. Root growth was also retarded. The typical, strong bending of the shoot noted by Sjollema[73] was seen in some specimens. Åberg suggested that the action of perchlorate was of a direct, physicochemical nature, in contrast to that of chlorate which he attributed to a specific mechanism involving "transformation" of the chlorate ion (possibly to hypochlorite[26]).

Ekdahl[26] further investigated the effects of various salts on the roots and root hairs of young wheat plants grown in water culture. He found that the toxicity of the chlorine compounds tested decreased in the following order: hypochlorite, chlorite > perchlorate > chlorate > chloride. Perchlorate in concentrations of 1 m*M* and 5 m*M* had only a weak effect on root hairs in 3 to 4.5 hr, although the result was somewhat greater than that produced by chlorate. No changes were noted in either the appearance of the root hairs or the intensity of the protoplasmic streaming. Since a 1 m*M* solution of perchlorate did not injure the roots after exposure for 24 hr, Ekdahl concluded that it was improbable that the perchlorate could have been reduced in the cells with formation of chlorate or hypochlorite, and that the action of perchlorate was of a direct nature.

In a broad survey of the toxicity of perchlorates in animals and plants, Durand[24] found that poppy, lentil and flax seeds germinated almost normally in 0.2 per cent sodium perchlorate solution, but were appreciably affected in 0.5 per cent solution. *Escherichia coli* and *Staphylococcus pyogenes aureus* were unharmed by 1 per cent sodium perchlorate; development was prevented by concentrations of about 2.5 to 3.0 per cent for *E. coli*, and 7.5 to 10 per cent for *S. aureus*. For the mold, *Sterigmatocystis nigra*, development was retarded below a concentration of 1.3 per cent (1:75) perchlorate; the weight of the mycelium was considerably diminished between 1.3 per cent (1:75) and 4 per cent (1:25), and development was prevented at a concentration of 10 per cent (1:10).

It is of interest to note in passing that Heidt[39] has investigated nonbiological photosynthesis in acidic perchlorate solutions. Perchlorate was used in this work because (1) it does not absorb visible or ultraviolet light, (2) has the smallest tendency of all negative ions in water to associate with other ions or molecules, and (3) is quite inert chemically in dilute solution. It is, Heidt states, the most inert, transparent isolationist that exists in dilute water solution.

ACTION OF PERCHLORATES IN ANIMALS

In 1868, Rabuteau[69] found that potassium perchlorate could be recovered unchanged in the urine, and he used the salt therapeutically against malaria. Sabbatini,[70] in a comparative study of the pharmacology of the oxygenated chlorine compounds, reported that, except for perchlorate, the toxicity generally decreased with decreasing oxidizing properties: hypochlorite > chlorite > perchlorate > chlorate (the same order of toxicity later found by Ekdahl[26] in wheat plants). The toxicity of perchlorate was attributed by Sabbatini to a sudden diminution of the potassium ion concentration (potassium-immobilization).

According to Kerry and Rost,[43] who described in detail the symptoms of perchlorate poisoning in various experimental animals, injection of from 0.015 g (minimum effective dose) to 0.030 g sodium perchlorate into frogs quickly resulted in fibrillation, twitching, and strong contraction (rigidity) of transversely striated muscle, radiating from the site of injection. The central nervous system was affected, as evidenced by greatly increased excitability of the reflexes even in decerebrated animals, and the heart was gradually paralyzed. The symptoms were less severe when the perchlorate was administered orally: although a dose of more than 0.05 g produced rigidity without the intervening muscular activity, recovery was complete when less than 0.15 g was administered.

In rodents (rats, mice, guinea pigs), sodium perchlorate produced increased reflex excitability, convulsions and tetany, often with opisthotonus. The symptoms appeared within 10 min after subcutaneous injection of 0.1 g perchlorate in rats, while 0.22 g resulted in death after 10 hr. A subcutaneous dose of 0.025 g was lethal for mice, and 1.35 g for guinea pigs; 2.9 g given orally proved fatal to a guinea pig in about 6 hr. Rabbits were unaffected by 0.4 g subcutaneously, 1.35 g intravenously (no change in blood pressure), or feeding of 1.0 g/day for some time (duration not stated). However, a single oral dose of 1.5 g in 4.5 per cent solution produced death in about 3 hr; numerous dot-like hemorrhages were found in the cecum on autopsy.

A pigeon, injected (partly intramuscular, partly into the crop) with doses of up to 0.22 g perchlorate, developed only mild symptoms but died in 18 hr. A dog, unaffected by the subcutaneous injection of 1.5 to 2.2 g, developed slight paralysis after oral administration of 4.40 g in 5.5 per cent solution. Subcutaneous injection of 1.5 to 2.2 g in cats produced definite disturbances. Vomiting followed (in 30 min) an oral dose of 2.75 g (in 50 ml of solution); a later intravenous injection of about 2.5 g (in 45 ml of solution) in the same animal produced slight paralysis, spastic rigidity, twitching and subsequent reflex excitability with tetany, clonic convulsions and death (in about 20 hr).

Part of the perchlorate administered intravenously to a rabbit was recovered unchanged in the urine by separation as the tetramethylammonium salt.[43]

Messini used the isolated gastrocnemius of the frog to study further the pharmacodynamic effects on striated muscle[59]; the action on smooth muscle was examined with giunea pig and cat uterus, the lower part of the cat esophagus, and the frog stomach.[60] The muscle contractions produced by addition of sodium perchlorate to the perfusion fluid were relieved by amounts of potassium chloride smaller than those known to inhibit muscle excitability, and, conversely, increased muscle tone from high doses of potassium chloride was diminished by sodium perchlorate. On the other hand, calcium and magnesium chlorides relieved perchlorate contractions only in doses larger than those known to suppress muscle excitability. The contraction-relaxation sequence from excess perchlorate ion and potassium

ion, respectively, could be repeated on muscle washed with sodium chloride solution.

In agreement with Sabbatini,[70] Messini attributed these phenomena to a disturbance of potassium ion equilibrium within the muscle, not by simple precipitation of potassium as the perchlorate, but rather by reduction of its thermodynamic activity. The equilibrium is restored by addition of small amounts of potassium chloride.

Cartolari[20] confirmed the reciprocal antagonism of perchlorate and potassium on the isolated frog heart. The action of perchlorate was similar, although more intense, than the effect of a potassium deficiency in the perfusion fluid. Small doses of perchlorate diminished the tone of the heart and the amplitude of its pulsations, while large doses produced transitory, grouped pulsations. Spagnol[82] concurred that perchlorate produces a decrease in the potassium ion concentration in the blood with a consequent change in the Ca:K ratio. He found that injection of sodium perchlorate into animals caused a depression of the parasympathetic-vagal system; high doses produced complete paralysis. The sympathetic system became hyperexcitable, with excessive sensitivity to adrenalin.

Eichler,[25] however, contended that the symptoms of perchlorate poisoning in frogs, which generally resembled the effects of thiocyanate, were more akin to those from an excess rather than a deficiency of potassium. Furthermore, he reported that perchlorate-poisoned frog hearts were cured by addition of calcium ion, but not by potassium. Cartolari[20] strongly contested this conclusion on the basis of his own observation that addition of perchlorate was beneficial rather than harmful to the frog heart poisoned by potassium chloride.

Boehm[11, 12] who investigated the reaction of sodium and potassium perchlorates on transversely striated muscle (frog sartorius), noted the occurrence of two contractions: a transient first contraction immediately following immersion in the isotonic test solution and gradually diminishing during 5 to 10 min; then a second one, beginning after the lapse of several minutes, which reached a maximum in about 15 min and lasted for more than an hour. Calcium chloride largely prevented the first contraction and delayed completion of the second contraction. The effect of previous curarization of the muscle was not clear-cut, but addition of novocaine after the perchlorate completely suppressed the second contraction. The great similarity of the effects of perchlorate to those produced by fluoborate was attributed by Boehm to the similar structure of the two anions; fluosulfonate, however, failed to cause more than an initial slight contraction. Boehm related the contracting action of perchlorate and fluoborate to precipitation of albumin within the muscle.

Both Eichler[25] and Boehm[12] placed perchlorates beyond thiocyanates in the Hofmeister lyotropic (anion) series,[79] in which anions are arranged in an order related to the diameter of the ion and the interaction between the ion and the dipoles of the water molecules.

As mentioned above, Kerry and Rost[43] found that the oral administration of 1.5 g sodium perchlorate to a rabbit caused convulsions and death in 3 hours. Kahane[42] also explored the toxicity of sodium perchlorate in rabbits and fish. In the rabbit, intravenous injection of 89 mg/kg body weight (0.5 ml, 50 per cent solution) had no effect, but 370 mg/kg body weight (2 ml, 50 per cent solution) produced prostration and total paralysis of the hind quarters lasting 10 to 15 min. Intracardiac injection of 179 mg/kg body weight (1 ml, 50 per cent solution) also resulted in temporary paralysis of the posterior. No methemoglobin was found on spectroscopic examination of the blood, showing that reduction of perchlorate to chlorate did not occur (compare effects of perchloryl fluoride). Repeated intravenous injections of a total of 0.55 g sodium perchlorate (200 mg/kg) during 8 days caused diarrhea; on autopsy, there were no changes in the heart, kidney or intestines, but the liver showed numerous areas of caseation. Subcutaneous, then intramuscular, injection during 12 days of a total of 3.95 g (1795 mg/kg) perchlorate resulted in diarrhea, emaciation, necrosis of the tissue at the injection sites (4 injections of 10 per cent solution, 5 of 50 per cent solution) and, after 8 days, death. Here, also, extensive caseation of the liver was noted.

Goldfish were not affected after 3 days in 0.1 per cent sodium perchlorate.[42] At higher concentrations, the results were as follows:

Per cent $NaClO_4$	Deaths/Total	Exposure (hr)
0.2	1/5	24
0.5, 1	2/5	24
2, 4	3/3	10

Again, Kahane found no evidence of reduction of perchlorate to either chlorate or chloride.

Durand[24] reported signs of paralysis in a rabbit sacrificed 2 hours after oral administration of 2 g sodium perchlorate, a dose which Eichler[8] had found to be fatal. Lest the amounts of perchlorate cited be considered as being precise, it may be noted that there is some discrepancy in Durand's statements about the toxic effects of perchlorate injected intramuscularly in the rabbit. On the one hand, he referred to a dose of 0.5 g as harmless but 1 g as toxic and fatal; he then described in detail the symptoms resulting from injection of 0.5 g (263 mg/kg), including muscle contraction, paralysis, tetany, and death in 4 days. Autopsy of the latter animal revealed the following: minor local lesions and congestion at the site of injection, and hepatisation of the lungs; the sciatic nerve, kidney, intestine, liver and brain were intact.

Tadpoles immersed in perchlorate solutions of various concentrations were affected after 48 hr in 0.1 per cent solution (3/5 dead); all (5/5) were dead after 36 hr at 0.2 per cent and 0.5 per cent, after 24 hr at 1 per cent and after 12 hr at 2 per cent. Leeches similarly treated were unharmed after 5 days in 0.5 per cent perchlorate; 2/3 were dead after 2 days at 1 per cent, 5/5 after 24 hr at 2 per cent, and 5/5 after 1 hr at 4 per cent.

Durand[24] also extended the studies of Rabuteau,[60] Kerry and Rost,[43] and Eichler[25] on the elimination of perchlorate in the urine. Eichler[25] reported that 75 per cent of the potassium perchlorate taken orally by man was eliminated in 24 hr, and up to 95 per cent in 72 hr, with a total recovery of 85 to 95 per cent. Durand[24] made the following observations of the fate of 0.784 g sodium perchlorate in 100 g water ingested by a normal human subject:

1. Perchlorate appeared in the urine 10 min after ingestion.
2. The maximum concentration of perchlorate occurred at about the third hour. The rate of elimination was: 30 per cent in 3 hr; 50 per cent in 5 hr; 85 per cent in 24 hr; 95 per cent in 48 hr.
3. All of the perchlorate ingested (within experimental error) was recovered. There was no chemical evidence of reduction of perchlorate to chlorate.

Distribution of sodium perchlorate throughout the rabbit body was also rapid[24]; it was found in all of the organs tested within 20 min after intravenous injection. Although the concentration in the same organ varied somewhat, depending on the route of administration (intravenous, intramuscular, oral) and on the time allowed for distribution (20 to 130 min), three broad categories were suggested by Durand from the data of three experiments:

1. Average concentration less than 100 mg sodium perchlorate/100 g tissue: heart, liver, lungs, kidneys, brain, blood, gastric mucosa, muscle, bone, testes (one experiment).
2. Average concentration 100 to 200 mg/100 g tissue: spleen, gall bladder, intestinal mucosa.
3. Higher concentrations (per 100 g tissue): ovaries, 445 mg; adrenal glands, 900 mg; urine, 640 mg.

It is unfortunate that the toxic symptoms and treatment of chlorate poisoning as given in the sixth edition of Sollmann's "Manual of Pharmacology"[77] are incorrectly attributed by Van Arsdell[87] to perchlorate. The same description of the toxic effects of swallowing large amounts of chlorate has been repeated in the eighth edition of Sollmann's work.[81] Actually, in many years of large-scale industrial production of various perchlorates —particularly the sodium, potassium and ammonium salts—no report has been found of any case of perchlorate intoxication.

The so-called irritating effect of perchlorates may also be in error. Except for the well-known corrosive (biological) or irritating effects of perchloric acid, no published information has been found which would confirm the following statement by Sax[71]: "Perchlorates are unstable materials, and are irritating to the skin and mucous membranes of the body whenever they come in contact with it. Avoid skin contact with these materials."

Schwartz[72] also lists perchlorates in a table of known primary skin irritants, but without any supporting data. Possibly the irritant effects of the alkali metal chlorates have been incorrectly attributed to the alkali metal perchlorates, and thence, by generalization, extended to all the perchlorates.

Because of the current interest in perchlorates as oxidizers in rocket propellants, some mention should be made of the possible hazard from inhalation of their combustion products. Feinsilver *et al.*[32] have investigated the inhalation toxicity in rats and mice exposed to the discharge gases of propellant mixtures containing various amounts of perchlorate; some of these compositions also contained sulfur. The discharge gases from all of the propellants contained carbon monoxide and hydrogen chloride; in addition, the mixtures containing sulfur discharged sulfur dioxide and hydrogen sulfide. All of these combustion products caused severe respiratory damage. The test animals which were dead or sacrificed immediately after exposure exhibited pulmonary edema, pulmonary hemorrhage, tracheitis and pneumonitis (with and without necrosis), and combinations of these. Extrapolation of the data by the authors indicated that a man exposed to the gases from a 400 g charge in a 20 m^3 chamber would be endangered in 30 to 60 min.

Although not mentioned by Feinsilver *et al.*[32] as occurring in their study, nitrous oxide, N_2O, nitric oxide, NO, and nitrosyl chloride, NOCl, have been found among the products of the thermal decomposition of ammonium perchlorate (see Chapter 3). In patenting the use of ammonium perchlorate explosive compositions, Carlson[18] stated that the decomposition on explosion proceeded according to the equation:

$$NH_4ClO_4 \rightarrow 2H_2O + NO_2 + Cl$$

With 3.5 per cent added carbon, he formulated the decomposition as:

$$3NH_4ClO_4 + C \rightarrow 6H_2O + CO_2 + N + 3Cl + 2NO_2$$

More reliable information has been provided by Bircumshaw and coworkers[8, 9, 10] who reported that the main products of the thermal decomposition of ammonium perchlorate are:

below 300°C

$$2NH_4ClO_4 \rightarrow Cl_2 + 3/2O_2 + 4H_2O + N_2O$$

above 300°C

$$2NH_4ClO_4 \rightarrow Cl_2 + O_2 + 4H_2O + 2NO$$

At higher temperatures, both nitrous and nitric oxides are formed, but the nitric oxide reacts with the chlorine and is analyzed as nitrosyl chloride. In a run at 420°C, gas analysis of the products gave the following results[62]:

$$10NH_4ClO_4 \rightarrow 2.5Cl_2 + 2N_2O + 2.5NOCl + HClO_4 + 1.5HCl + 18.75H_2O + 1.75N_2 + 6.375O_2$$

The corrosive action of perchloric acid is discussed later in this chapter. The hazards from inhalation of hydrogen chloride and chlorine are well known and need not be elaborated. Nitrosyl chloride is included among the respiratory irritants.[28] In a detailed review of the toxicity of the oxides of nitrogen, Gray[40] notes that nitrous oxide, N_2O, is considered to be dangerous only in high concentrations (approaching 90 per cent), and then principally from anoxia; nitric oxide, NO, appears to be only about one-fourth to one-fifth as toxic as nitrogen dioxide, NO_2. Nevertheless, the possibility should not be excluded that a hazard from nitrogen oxides may occur when ammonium perchlorate is decomposed under appropriate conditions.

Effect of Perchlorate on the Thyroid Gland

It has been demonstrated that thiocyanate intereferes with the collection and concentration of iodide ion in the thyroid gland.[7, 88] The separate process of hormone synthesis, in which iodide is combined with tyrosyl groups, is prevented by thiourea and related compounds such as propylthiouracil, methylthiouracil, and 1-methyl-2-mercaptoimidazole.[5, 6, 41, 58, 84] Wyngaarden, Wright and Ways[95] found that the monovalent anions perchlorate, chlorate, hypochlorite, periodate, iodate, biiodate and nitrate share with thiocyanate the properties of inhibiting collection and interfering with retention of iodide in the thyroids of rats chronically treated with proplythiouracil. The blocking effect of perchlorate on the thyroid appears also to extend to other iodide-concentrating mechanisms of the animal body.[87]

Perchlorate, periodate, iodate and chlorate produced the quantitative discharge of iodide from rat thyroids, but only perchlorate did so within 15 min.[95] In this respect, perchlorate was about 10 times more effective than thiocyanate, and approximately 300 times more than nitrate, in discharging radioiodide; hypochlorite and biiodate were intermediate in potency. Investigation of the ability of these substances to prevent the accumulation of iodide showed them approximately to parallel their iodide-discharging action, with perchlorate again the most effective. Rats treated with perchlorate for 17 days developed hyperplastic, colloid-depleted, low-iodine goiters. The changes were as marked as those resulting from ingestion of propylthiouracil.

Halmi and Stuelke[36] reported that, while subcutaneous injection of 100 mg or more of sodium perchlorate prevented active uptake of I^{131} by the thyroid glands of rats treated with propylthiouracil, all of the trapped I^{131} was not discharged if the perchlorate was given after I^{131} administration. The longer the interval between the injection of I^{131} and sodium perchlorate, the smaller the amount of I^{131} which could be discharged. The non-dischargeable I^{131} did not appear to be bound to thyroglobulin.

A study was made of the effects in the rat of increasing quantities of iodide, thiocyanate, perchlorate and nitrate on the ability of the thyroid gland to concentrate radioiodide.[94] All of these anions produced a marked reduction of the radioiodide concentration gradient between thyroid and serum. Here, again, perchlorate was the most potent anion, and nitrate the least; iodide and and thiocyanate were intermediate and of approximately equal effectiveness on a molar basis.

As a result of further animal studies, Krüskemper and Kleinsorg[48] suggested, contrary to the opinion of the group at the Massachusetts General Hospital,[95] that perchlorate interferes with the synthesis of thyroxine. They reported that potassium perchlorate reduced the respiration of the liver in normal rats[48] and mice,[44] but there was no effect on tissue respiration in vitro and no peripheral antagonism to thyroxine. In hypophysectomized rats, potassium perchlorate suppressed the metabolic increase produced by thyrotropic hormone, and the enlargement of the thyroid gland found in normal animals did not appear even at a dosage level of 250 mg/kg/day.[44] The effects on metabolism and weight of the thyroid gland produced by administration of 250 mg/kg/day of potassium perchlorate for 14 days were the same as from 100 mg/kg/day of methylthiouracil; there were no toxic effects. The results in mice were similar: doses of 100 mg/kg/day perchlorate alone decreased liver respiration and increased thyroid weight, although the effects of simultaneously injected thyroxine on metabolism and thyroid weight were not altered.[44] Breslavskiĭ and Simon[13] obtained qualitatively similar results in rats; they reported, however, that the uptake of radioiodide and the increase in weight of the thyroid glands were markedly smaller in animals treated with potassium perchlorate than in those receiving equimolar doses of methylthiouracil.

In a study of the effect of thyroxine and antithyroid substances (potassium perchlorate and methylthiouracil) on the serum protein in rats, Kleinsorg and Krüskemper[45] noted that thyroxine (3 mg/kg/day for 10

days) decreased the serum protein from 6.93 gram-per cent to 5.61 gram-per cent. There was no change when potassium perchlorate (100 mg/kg/day) was fed simultaneously, but the albumin decreased by 21.5 per cent and the globulins by 15 per cent (α, β and γ at the same rate). Potassium perchlorate alone, fed at 100 or 250 mg/kg/day, raised the β-globulin content by 68 per cent in 14 days, and 94 per cent in 28 days, while the albumin/globulin ratio was lowered from 1.8 to 1.17. Methylthiouracil, at 100 mg/kg/day, raised the β-globulin by 79 per cent and lowered the albumin/globulin ratio to 1.37. In the latter two cases, there was very little, if any, change in albumin content, but total protein increased from 7 to 15 per cent.

Oral administration of 3 to 500 mg doses of potassium perchlorate to thyrotoxic (Graves' disease) human subjects pretreated with 1-methyl-2-mercaptoimidazole resulted in the rapid release of previously accumulated iodide from the thyroid.[83] No toxic effects of perchlorate were seen at this dosage level (total of not more than 600 mg). Like thiocyanate, perchlorate inhibited the accumulation of I^{131}; Brügel[15] found that the amount taken up was reduced to less than 1 per cent of the normal amount. The period of inhibition after a single dose of 100 mg perchlorate was about 6 hr,[83] within which time, as demonstrated by Durand,[24] a little more than half of the perchlorate administered would have been eliminated in the urine. Subsequently, hyperthyroidism was also successfully controlled in 24 patients treated with oral doses of 200 to 400 mg potassium perchlorate every 8 hours.[83] Symptoms improved and the basal metabolic rate and serum concentration of protein-bound iodine returned to normal. The only toxic manifestations were seen in two of the patients who developed irritation of the gastrointestinal tract, which the authors felt might have been due to the perchlorate. There were no significant changes in the formed elements of the blood and no evidence of liver damage, although some patients were treated for as long as 52 weeks. The authors concluded, therefore, that potassium perchlorate was an effective antithyroid agent in the preoperative continuous treatment of thyrotoxicosis, and of particular value in those patients who may be sensitive to or fail to respond to drugs of the thiourea group or iodide.

Confirmatory results in 15 hyperthyroid patients were obtained by Kleinsorg and Krüskemper.[46] At oral dosage levels of 0.8 to 1.2 g potassium perchlorate per day for up to 4.5 months, the basal metabolism fell to nearly normal, body weight increased, and blood cholesterol increased to normal.[47]

Effects of Perchloric Acid

The extensive use of perchloric acid as an analytical reagent has been discussed in Chapters 2 and 7. The cold 70 to 72 per cent aqueous solution has no oxidizing power; it acts as a strong acid and exhibits the reactions of the hydrogen ion. The hot, concentrated acid, however, is a strong oxidizer and dehydrating agent. Like other strong acids, perchloric acid in the form of liquid, mist or vapor is highly corrosive to the skin, eyes and mucous membranes. The amount of damage will depend upon the concentration, temperature, and duration of contact.

Perchloric acid is considered to be a primary skin irritant: i.e., a substance that causes dermatitis by direct action on the normal skin at the site of contact if it is permitted to act in sufficient concentration or quantity for a sufficient length of time.[66, 72] A primary skin irritant may also be a sensitizer: i.e., a substance that does not necessarily cause demonstrable skin changes on first contact, but effects such specific changes in the skin so that, after 5 to 7 days or more, further contact (of the same substance) on the same or other parts of the body will cause dermatitis.[66, 72] While no cases of sensitization specifically attributed to perchloric acid appear to have been described, the possibility that this may occur in certain individuals should not be excluded.

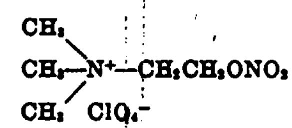
Since perchloric acid is not very volatile, the types of injury most likely to occur in industry are irritation of the respiratory tract through inhalation of the mist or spray, and severe burns of the eyes and skin through contact with the liquid. No reports of accidental ingestion of perchloric acid have been found in the literature.

The simple precautions to be followed in handling perchloric acid are briefly stated in a number of publications.[4, 31, 38, 56, 61] Like other strong acids, perchloric acid should not be pipetted by mouth suction. Since protection of the eyes and skin is essential, at least chemical safety goggles and rubber gloves should be worn. Personnel handling quantities of perchloric acid should be provided with chemical safety goggles, rubber gloves, rubber sleeves, rubber apron, and rubber safety-toe boots or shoes. Deluge showers and eye-washing fountains should be provided in all working and storage areas. Clothing contaminated with perchloric acid is highly flammable and should be removed and washed thoroughly with water. In case of accidental contact with perchloric acid, the skin or eyes should be flushed immediately with large quantities of water for at least 15 min; any contact with the eye should receive prompt medical attention.

The requirements for packaging, labeling and shipping perchloric acid are discusssed in Chapter 11.

Effects of Nitrate Ester of Choline Perchlorate

The pharmacology of the nitrate ester of choline perchlorate, has been examined by Carr *et al.*[19] This compound is a stable, white, crystalline ma-



terial, melting point 188 to 189°C, easily recrystallized from water. The solubility in water is 0.82 g/100 ml at 20°C; the pH of a 0.1 per cent solution is between 6 and 7.

Two drops of a 1 per cent solution of the nitrate ester of choline perchlorate dropped into the rabbit eye caused strong pupillary constriction (miosis) within 10 min; this was antagonized by atropine. In comparison, choline and nitrosocholine do not produce miosis. At a concentration of $1:10^5$, the depressor activity was about one-half that of acetylcholine; this effect was obliterated by atropine but not by cholinesterase. The contracting effect in vitro on the frog pylorus was greater than that from acetylcholine ($1:2.5 \times 10^6$). Injection of 1 to 40 mg/100 g body weight in rats produced chromodacryorrhea ("bloody tears") within 1 min which was obliterated by intraperitoneal injection of atropine sulfate (10 mg/100 g). The LD_{50}* (1 hr) by intraperitoneal injection in the rat was found to be 25 mg/kg body weight; the nitrate ester of choline perchlorate is, therefore, approximately 10 times more toxic than acetylcholine. The deaths from its administration were much more prompt than those caused by acetylcholine; convulsions, which occurred within 3 min (at lethal doses) and lasted no longer than 1 min were clonic and characterized by marked emprosthotonus.

Effects of Perchloryl Fluoride

Perchloryl fluoride, ClO_3F, is included in this review of the biological action of perchlorates since the infrared vibrational,[52] rotational[54] and microwave[51] spectra support the perchlorate type of tetrahedral structure with the fluorine and oxygen atoms bonded directly to chlorine. It appears to be the first perchlorate to have been subjected to the current systematic technique of acute toxicity screening in laboratory animals which has proved so valuable in establishing modern industrial hygiene, precautionary labeling and shipping standards.[17, 27, 40, 57, 64] The chemical and physical properties of perchloryl fluoride are discussed in Chapter 5.

Greene *et al.*[35] and Kunkel[49] have reported the effects in rodents and dogs of single and repeated exposure to perchloryl fluoride. The gas was metered from a cylinder at room temperature into a dynamic exposure chamber. In rodents exposed for a single 4-hr period, the LC_{50}† was found

* LD_{50} = amount which kills 50 per cent of a group of test animals.

† LC_{50} = concentration of a gas which kills 50 per cent of a group of test animals exposed for a given period of time.

to be 385 ppm (1610 mg/m³)* for male rats and 630 ppm (2640 mg/m³) for female mice. Most of the deaths occurred during exposure and none later than 2 days after exposure.

Dogs similarly exposed for a single 4-hr period to 224 ppm and 524 ppm perchloryl fluoride developed cyanosis and hyperpnea. At concentrations of 451 ppm (for 4 hr) and 622 ppm (for 2.5 hr), the dogs became seriously ill, showing cyanosis, hyperpnea, convulsions and emesis; these animals died unless treated with methylene blue after exposure. All of the dogs developed methemoglobinemia which disappeared within 1 to 5 days after exposure

In rodents repeatedly exposed for 6 hr/day, 5 days/week to 185 ppm perchloryl fluoride, the mortalities were 10/10 guinea pigs in 3 days, and 18/20 rats and 20/29 mice after 7 weeks.[35] All the animals showed slight cyanosis and polypnea, with occasional cases of exophthalmos. The rats, which were examined in greater detail, were found to have developed methemoglobinemia during the first week of exposure, but after the second week methemoglobin and hemoglobin values approached normal levels. When these subacute exposure experiments were repeated for 5 weeks at a concentration of 100 ppm, 1/20 rats and 10/10 guinea pigs died within 2 weeks; the blood picture was essentially the same as that found at 185 ppm.[49]

In addition to pulmonary irritation, methemoglobinemia, and a decrease in total hemoglobin in both rodents and dogs, the authors also report[35] an increased fluoride content of the blood, hemosiderosis (indicating hemolysis during exposure) and increased hematopoietic activity (the spleens were considerably enlarged). Other investigators are cited as having observed similar effects with larger quantities of perchloryl fluoride,[14, 68] or more severe effects at the same exposure level using static exposure chambers.[68] Exposure of rats and monkeys to as little as 40 ppm for 3 months produced enlarged spleens and lungs with some evidence of red cell destruction, although there were no external signs of damage.[68]

Despite its perchlorate structure, the physiological activity of perchloryl fluoride thus appears to be more like that of chlorate than of perchlorate with respect to the formation of methemoglobin. The oxidation of hemoglobin (ferrous iron) to methemoglobin (ferric iron) can be accomplished in vitro by a number of oxidizing agents, but only chlorate is said to do so in vivo.[78] The typical formation of methemoglobin and the destruction of red corpuscles by chlorate are cited by Sollmann.[80] However, Eichler,[25] Kahane[42] and Durand[24] found no evidence of methemoglobin formation after administration of sodium or potassium perchlorate.

*At 25°C and 760 mm Hg:

$$1 \text{ ppm} = \left(\frac{\text{mol. wt.}}{24.45}\right) \text{mg/m}^3$$

Pennsalt Chemicals Corporation[67] states that no injuries have occurred during a number of years of laboratory and plant experience with perchloryl fluoride. A tingling sensation is said to be felt on exposed skin surfaces, but the gas is not irritating to the skin or eyes. Frostbite can, of course, occur from contact of the skin with the low-boiling (−46.8°C) liquid.

It has been pointed out[67] that, using LC_{50} = 385 ppm (1610 mg/m³) for rats[35] as a basis for estimating its acute vapor toxicity toward man, perchloryl fluoride would be rated as "moderately toxic" under the classification scheme of Hodge and Sterner.[40] For comparision, acrylonitrile and hydrogen cyanide fall into the same general category, but the analogy should be carried no further. No hygienic standard for daily inhalation[76] of perchloryl fluoride has yet been established—i.e., the time-weighted average concentration (threshold limit, MAC) during a normal work day to which workers may be repeatedly exposed.[3]

Elkins,[29] in reviewing the criteria to be used in setting MAC values, recommends that, when the only data available are from animal experiments, the MAC should not exceed one-fifth the lowest concentration found to affect animals seriously on continued exposure. Since, as noted above, repeated exposure of animals for 3 months to as little as 40 ppm perchloryl fluoride has produced histopathological changes,[68] an MAC of one-fifth this concentration might very well be too high. The picture is further complicated by the demonstration of increased fluoride in the blood of exposed rodents.[35] If the MAC for perchloryl fluoride were to be based upon its fluorine content and the corresponding ACGIH threshold limit[3] for fluoride of 2.5 mg/m³, then the value should not exceed 3 ppm (13 mg/m³) perchloryl fluoride.

It is thus evident that those handling perchloryl fluoride should be adequately protected against inhalation, skin contact and ingestion. Since perchloryl fluoride is said to have a mild, sweetish odor detectable at about 10 ppm in air,[67] this may be used to warn of exposure although the development of nasal fatigue should not be overlooked.[65] No analytical methods have yet been developed specifically for the determination of small amounts (parts per million) of perchloryl fluoride in air. Although this compound is unusually stable to aqueous hydrolysis, the rapid hydrolyis in alcoholic potassium hydroxide might be used as the basis for a modification of one of the existing procedures for the determination of fluoride in air.[23, 30, 86, 93]

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11. SAFETY CONSIDERATIONS IN HANDLING PERCHLORATES

As a general rule, perchloric acid and the perchlorates must be considered to be hazardous substances, and they should be handled with due respect for the damage to persons and property which may result from misuse or carelessness. However, the extensive and growing uses for these extraordinary chemicals suggest that the very properties which make them so valuable become the source of accidents only when the appropriate precautions are not taken. The information and recommendations presented in this chapter are not intended to provide recipes to be followed rigidly by the prospective user of perchloric acid or perchlorates, but rather to form the basis for a careful evaluation of the potential hazards involved in any proposed operating procedure.

PERCHLORIC ACID

Perchloric acid literally burst into international attention on February 20, 1947, when a violent explosion in Los Angeles, California, at the O'Connor Electro-Plating Corporation resulted in the death of 17 persons and wrecked 116 buildings with damages estimated at $2,000,000. Newspaper accounts of the accident described grim military patrols of the devastated area and even hinted that fissionable materials (a mushroom-shaped cloud was released) were to blame for the reportedly 1,000 injured and 64 dead. A calmer appraisal of the evidence by a coroner's jury[57] and by the U. S. Bureau of Mines[9] revealed that the explosion was caused by a mixture for the electropolishing of aluminum, consisting of approximately 150 gallons of 68 to 72 per cent perchloric acid and 70 gallons of acetic anhydride into which a plastic holder had been introduced. Furthermore, the refrigeration system for the stainless steel tank (phenolic resin-coated) had been shut off. As will be shown, it would have been rather surprising if an explosion had not taken place.

The great usefulness of perchloric acid, a virtually irreplaceable reagent in analytical chemistry, should not obscure the fact that it is a hazardous substance. But perchloric acid, like many other hazardous materials, can be used safely in a variety of ways and in quantities ranging from milligrams to hundreds of pounds, provided that its properties are understood and its hazardous character is recognized.

The physical and chemical properties of anhydrous and aqueous perchloric acid have been described in Chapter 2. The highly corrosive action